

ANNUAL PROGRESS REPORT

Report Prepared by Dr. Henry Lardy

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ANNUAL RATE: \$10,000, including overhead.

CONTRACTOR: University of Wisconsin.

PRINCIPAL INVESTIGATOR: Dr. Henry Lardy

Assistants: Dr. Lafayette Noda, Dr. Gladys Maley, Dr. Kenkichi Tomita.

TITLE OF PROJECT: Studies on the Mechanism of Hormone Action.

SUMMARY OF RESULTS

a. Since start of project.

Work on in vitro effects of thyroid hormones on enzymatic systems carrying out oxidative phosphorylation has been completed and published. Uncoupling of phosphorylation from respiration was obtained with triiodothyronine using rat kidney mitochondria. This has since been confirmed using both guinea pig and chick tissue.

b. During current report period.

The purification of ATP-creatine transphosphorylase has been completed as described in our last semiannual report to ONR. In addition, kinetic and equilibria studies have been made. The most interesting finding was that free ATP and ADP are not participants in the transphosphorylation reaction but that the Mg-complexes of these nucleotides are the "active" forms.

In agreement with an earlier report of Askonas, thyroxine was found to inhibit the enzyme but the effect appeared to be due entirely to its complexing with Mg^{++} . Excess Mg^{++} overcomes the inhibition.

A study of the solubility product of the Mg-thyroxine complex was therefore undertaken. A value for $SP = 10^{-17}$ indicates that very little of the hormone will remain in solution if any appreciable amount of Mg^{++} is present.

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Additional work on various aspects of the thyroid hormone problem is in progress.

The work of Dr. Pressman (which was described in the semiannual report) is being prepared for publication.

PLANS FOR FUTURE:

An examination of several enzymatic changes in whole animal tissues resulting from increased or decreased activity of the thyroid gland is being made. This work will continue until we are able to interpret these changes in terms of the function of the thyroid hormone. Additional work will be done on in vitro effects of thyroid hormones on tissues from species which are not susceptible to the action of the hormone. This should tell us whether the fault^{is} in the tissues or in the inability to convert thyroxine to the "active" hormone.

Chemical work will also be done in an attempt to find out what the "active" hormone is. It seems likely that triiodothyronine is closer to the active compound than thyroxine but much information indicates that triiodothyronine is not the agent responsible for the true activity of the hormone in vivo.

REPORTS AND PUBLICATIONS

1. Metabolic Effects of Thyroid Hormones in vitro. II. Influence of Thyroxine and Triiodothyronine on Oxidative Phosphorylation. Maley, J. F., and Lardy, H. A., J. Biol. Chem. 204, 435 (1953).
2. Adenosinetriphosphate-Creatine Transphosphorylase. I. Isolation of the Crystalline Enzyme from Rabbit Muscle. S. A. Kuby, L. H. Noda, and H. A. Lardy. Submitted to J. Biol. Chem.
3. Adenosinetriphosphate-Creatine Transphosphorylase. II. Homogeneity Studies and Physical-Chemical Properties. L. H. Noda, S. A. Kuby, and H. A. Lardy. Submitted to J. Biol. Chem.
4. Adenosinetriphosphate-Creatine Transphosphorylase. III. Kinetic Studies. S. A. Kuby, L. H. Noda, and H. A. Lardy. Submitted to J. Biol. Chem.

5. Adenosinetriphosphate-Creatine Transphosphorylase. IV. Equilibrium Studies.
L. H. Noda, S. A. Kuby, and H. A. Lardy. Submitted to J. Biol. Chem.
6. Metabolic Effects of Thyroid Hormones in Vitro. Lardy, H. A., and Maley, G. F.
Progress in Hormone Research, Vol. 9. In Press. (1954).